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(54) **PYRAZOLO 1,5-a]PYRIMIDINE DERIVATIVE AND ANTI-INFLAMMATORY CONTAINING THE SAME.**

(57) Pyrazolo[1,5-a]pyrimidine derivatives represented by general formula (I), wherein R_1, R_2, R_3 and R_4 represent each hydrogen, carboxyl, lower alkoxycarbonyl, phenyl, or lower alkyl or cycloalkyl which may be each substituted with hydroxy, carboxyl or lower alkoxycarbonyl, or alternatively R_1 and R_2 maybe combined together to form lower alkylene; R_5 represents $-SR_6$ or $-NR_7R_8$; R_6 represents pyridyl or phenyl which may be substituted with one to three groups selected from among hydroxy and lower alkyl and R_7 and R_8 represent each hydrogen or phenyl which may be substituted with one to three groups selected from among hydroxy, lower alkyl, lower alkoxycarbonyl and carboxyl, or alternatively R_7 and R_8 may be combined to form, together with the nitrogen atom to which they are bound, 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, phenyl which may be

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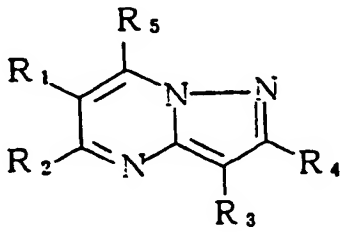
substituted with halogen or trihalomethyl, or 1-piperazinyl which may be substituted with hydroxy-lower alkyl or diphenyl-lower alkyl, salts thereof, and an anti-inflammatory containing as the active ingredient the compound with the above formula wherein R_1, R_3 and R_4 represent each hydrogen, R_2 represents lower alkyl or cyclo...yl, and R_5 represents $-NR_7R_8$ wherein R_7 represents hydrogen and R_8 represents phenyl substituted with hydroxy and two lower alkyl groups.

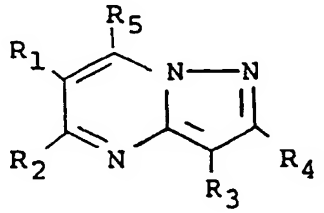


(I)

Technical Field

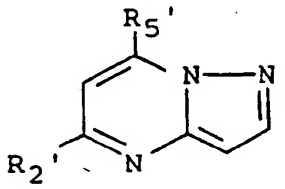
The present invention relates to novel pyrazolo[1,5-a]pyrimidine derivatives which are useful as medicaments, and an anti-inflammatory agent containing the same as an active ingredient.

More particularly, the present invention relates to a pyrazolo[1,5-a]pyrimidine derivative of the formula:



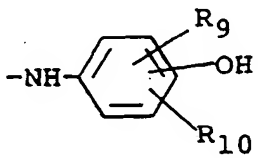
(I)

wherein R_1, R_2, R_3 and R_4 are the same or different and are each hydrogen atom, carboxyl group, a lower alkoxycarbonyl group, phenyl group, a lower alkyl group which may optionally be substituted by a group selected from hydroxyl group, carboxyl group and a lower alkoxycarbonyl group, or a cycloalkyl group, or R_1 and R_2 may combine each other to form a lower alkylene group; R_5 is a group of the formula: $-SR_6$ or a group of the formula: $-NR_7R_8$ in which R_6 is pyridyl group or a phenyl group which may optionally be substituted by 1 to 3 groups selected from hydroxyl group and a lower alkyl group; and R_7 and R_8 are hydrogen atom, a phenyl group which may optionally be substituted by 1 to 3 groups selected from hydroxyl group, a lower alkyl group, a lower alkoxycarbonyl group and carboxyl group, or R_7 and R_8 may combine each other to form with a nitrogen atom with which they bond 1-pyrrolidinyl group, 2-oxo-1-pyrrolidinyl group, or 1-piperazinyl group substituted by a phenyl group optionally being substituted by a halogen atom or a trihalomethyl group, a hydroxy-lower alkyl group or a diphenyl-lower alkyl group, or a salt thereof. Moreover, the present invention relates to an anti-inflammatory agent which contains as an active ingredient at least a compound of the pyrazolo[1,5-a]pyrimidine derivatives represented by the formula:



(I')

wherein R_2' is a lower alkyl group or a cycloalkyl group, R_5' is a group of the formula:



in which R_9 and R_{10} are each a lower alkyl group, or a salt thereof.

Background Art

Recently, it has been found that an arachidonic acid metabolite anticipates in inflammation. That is, arachidonic acid, which is one of the components comprising phospholipid existing on the cell membrane, may be released from the cell membrane by various stimulus, e.g. phlogogenic stimulus, antigen-antibody reaction (i.e. immuno-stimulation), etc., and then firstly metabolized by lipoxygenase or cyclooxygenase, etc., to be converted into various products. It has been proved that prostaglandin E_2 (PGE_2) and prostaglandin I_2 (PGI_2) which are produced by cyclooxygenase, or hydroxyperoxyeicosatetraenoic acids (HPETE) and hydroxyeicosatetraenoic acids (HETE) which are produced by lipoxygenase, anticipate in the

above inflammation.

On the other hand, there have been known some anti-inflammatory agents which exhibit their anti-inflammatory activity by specifically inhibiting the above mentioned cyclooxygenase, such as indomethacin, ibuprofen, and the like. However, these agents have some problems, for instance, they cannot easily permeate into the affected parts, and hence, it has been expected to develop new agents which exhibit a potent anti-inflammatory activity especially in the form of external medicine preparations.

The present inventors have found that the pyrazolo[1,5-a]pyrimidine derivatives having the above formula (I) and their salts show various pharmacological actions, that particularly the compounds having the above formula (I') show excellent enzyme inhibitory activities and potent anti-inflammatory activities based thereon, and have achieved the present invention.

An object of the present invention is to provide novel pyrazolo[1,5-a]pyrimidine derivatives of the above formula (I) which are useful as a medicament. Another object of the present invention is to provide an anti-inflammatory agent containing as an active ingredient the compound of the above formula (I'). The other objects and advantages of the present invention are apparent to any skilled person in the art from the following description.

Disclosure of the Invention

The novel pyrazolo[1,5-a]pyrimidine derivatives of the present invention have the above formula (I), and show various pharmacological activities, for example, ischemic-reperfusion disorder improving activity, anti-inflammatory activity, antirheumatic activity, activity for treatment of asthma, antiallergic activity, antipyretic and analgesic activity, etc., and hence, they are useful as a medicament such as drug for improving of ischemic-reperfusion disorder, anti-inflammatory agent, antirheumatic agent, drug for asthma, antiallergic agent, antipyretic analgesic, and the like, in animals, especially mammals. Moreover, the compound of the formula (I') is useful as anti-inflammatory agent based on excellent anti-inflammatory activity thereof.

Suitable examples of the groups in the above formulae (I) and (I') are as follows.

The "lower alkyl group" includes, for example, straight chain or branched chain alkyl groups having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, and the like.

The "lower alkoxycarbonyl group" includes, for example, straight chain or branched chain alkoxycarbonyl groups having 2 to 7 carbon atoms such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, and the like.

The "lower alkyl group which may optionally be substituted by a group selected from hydroxyl group, carboxyl group and a lower alkoxycarbonyl group" includes, for example, in addition to the above mentioned lower alkyl groups, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2-hydroxyisopropyl, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, butoxycarbonylmethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, and the like.

The "cycloalkyl group" includes, for example, cycloalkyl groups having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The "lower alkylene group" includes, for example, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, and the like.

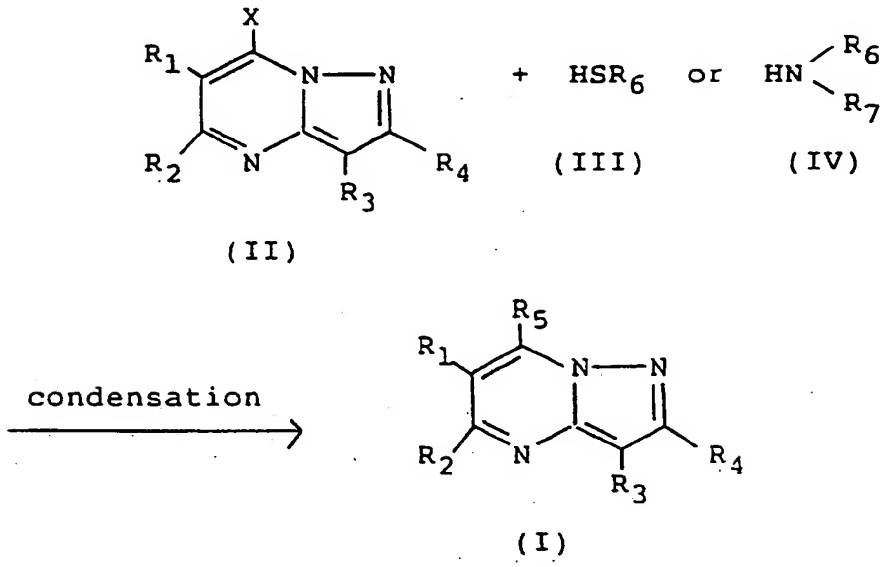
The "phenyl group which may optionally be substituted by 1 to 3 groups selected from hydroxyl group, a lower alkyl group, a lower alkoxycarbonyl group and carboxyl group" includes, for example, in addition to phenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2,3-dihydroxyphenyl, 2,4-dihydroxyphenyl, 3,4-dihydroxyphenyl, 2-methylphenyl, 1,3-dimethylphenyl, 3,4,5-trimethylphenyl, 3-ethylphenyl, 2,3-diethylphenyl, 2,4,6-triethylphenyl, 4-propylphenyl, 2,4-dipropylphenyl, 1,2,3-tripropylphenyl, 4-t-butylphenyl, 2,4-di-t-butylphenyl, 2,4,6-tri-t-butylphenyl, 3,5-di-t-butyl-4-hydroxyphenyl, 2-methoxycarbonylphenyl, 3-methoxycarbonyl-4-hydroxyphenyl, 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 2,4-dicarboxyphenyl, 2,4,6-tricarboxyphenyl, 3-carboxy-4-hydroxyphenyl, and the like.

The "phenyl group optionally being substituted by a halogen atom or a trihalomethyl group" includes, for example, in addition to phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-iodophenyl, 3-iodophenyl, 4-iodophenyl, 2-fluoro-3-chlorophenyl, 2-trifluoromethylphenyl, 3-trichloromethylphenyl, 4-tribromomethylphenyl, 2-triiodomethylphenyl, 3-difluoromonochloromethylphenyl, 4-monochlorodibromomethylphenyl, 2-dichloromonoiodomethylphenyl, and the like.

The "diphenyl-lower alkyl group" includes, for example, diphenylmethyl, 2,2-diphenylethyl, 2,3-diphenylpropyl, and the like.

The pyrazolo[1,5-a]pyrimidine derivatives of the present invention can be prepared by the following reaction schemes.

[Reaction Scheme-1]



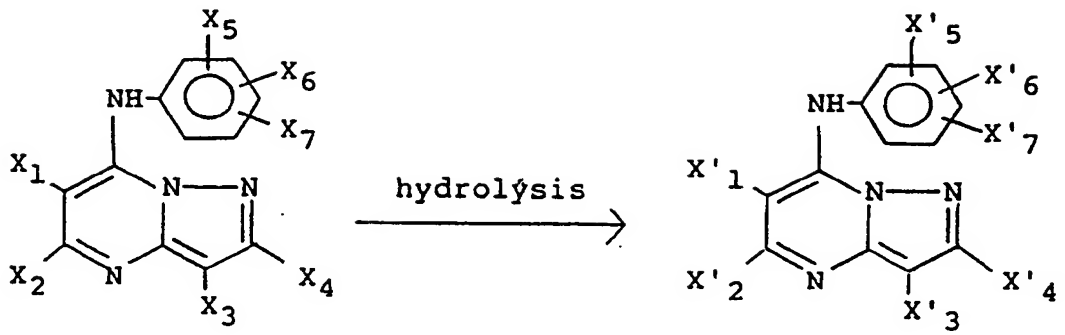
wherein X is a halogen atom, and R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are the same as defined above.

As shown in Reaction Scheme-1, the compounds (I) of the present invention can be prepared by the condensation reaction of a pyrazolo[1,5-a]pyrimidine halide derivative (II) and a thiol compound (III) or an amine compound (IV).

The above reaction is usually carried out in a suitable solvent in the presence or absence of an acid acceptor. The acid acceptor includes, for example, inorganic bases such as hydroxides, hydrogen carbonates and carbonates of alkali metals (e.g. NaOH, KOH, $NaHCO_3$, K_2CO_3, etc.), or tertiary amines such as triethylamine, dimethylaniline, diethylaniline, N-methylmorpholine, pyridine, 4-dimethylaminopyridine, and the like. The solvent includes, for example, inert organic solvents such as lower alcohols (e.g. methanol, ethanol, etc.) and ethers (e.g. tetrahydrofuran (THF), dioxane, etc.). When an inorganic base is used as an acid acceptor, it is preferable to use as a solvent a mixture of an inert organic solvent and water. Moreover, aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.) may also be used as a solvent.

In the above reaction, the ratio of the pyrazolo[1,5-a]pyridimidine halide derivative (II) and the thiol compound (III) or the amine compound (IV) is not specified, but the latter is used in an equimolar or excess amount to one mole of the former. The above acid acceptor is preferably used in an amount of equimolar or excess amount to one mole of the pyrazolo[1,5-a]pyrimidine halide derivative. The reaction is carried out either under cooling, at room temperature or under heating, but it is usually carried out at a temperature of 0 °C to a refluxing temperature of the solvent used therein, for 0.5 to 15 hours.

[Reaction Scheme-2]

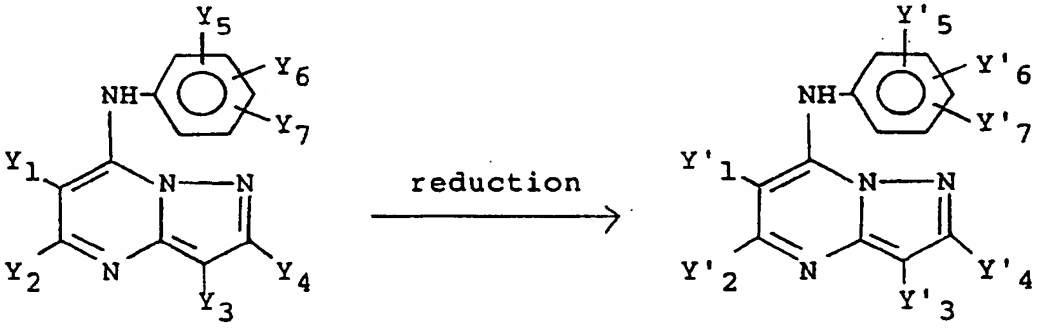


(Ia) (Ib)

wherein X_1 - X_7 and X'_1 - X'_7 are each the corresponding group in the above formula (I), that is, X_1 and X'_1, X_2 and X'_2, X_3 and X'_3, X_4 and X'_4 correspond to R_1, R_2, R_3 and R_4, respectively, and X_5 and X'_5, X_6 and X'_6, X_7 and X'_7 are hydrogen atom, hydroxyl group, a lower alkyl group, a lower alkoxycarbonyl group or carboxy group, provided that at least one of X_1, X_2, X_3, X_4, X_5, X_6 and X_7 is a lower alkoxycarbonyl group or a lower alkoxycarbonyl-lower alkyl group, and a group in X'_1, X'_2, X'_3, X'_4, X'_5, X'_6, X'_7, of which position is the same as that of the above group, is carboxyl group or a carboxy-lower alkyl group.

As shown in Reaction Scheme-2, one of the compounds of the present invention (Ib) can be prepared by hydrolysis of the compound (Ia) which is one of the compounds (I) prepared in Reaction Scheme-1 and has a lower alkoxycarbonyl group and/or a lower alkoxycarbonyl-lower alkyl group as a substituent. The above reaction is carried out in a mixed solvent of water and an inert solvent such as lower alcohols (e.g. methanol, ethanol, etc.), ethers (e.g. THF, dioxane, etc.) in the presence or absence of an alkali metal hydroxide (e.g. NaOH, KOH, etc.) and sodium hydrosulfate ($Na_2S_2O_4$) in an amount of 1 to 30 moles to one mole of the compound (Ia). When one of X_5, X_6 and X_7 is OH group positioning at p-position to the NH group, said OH group possibly be oxidazed during the hydrolysis, and hence, the reaction is preferably carried out in the presence of $Na_2S_2O_4$. The reaction may proceed either under cooling, at room temperature or under heating, but it is usually carried out at a temperature of 0°C to a refluxing temperature of the solvent used.

[Reaction Scheme-3]



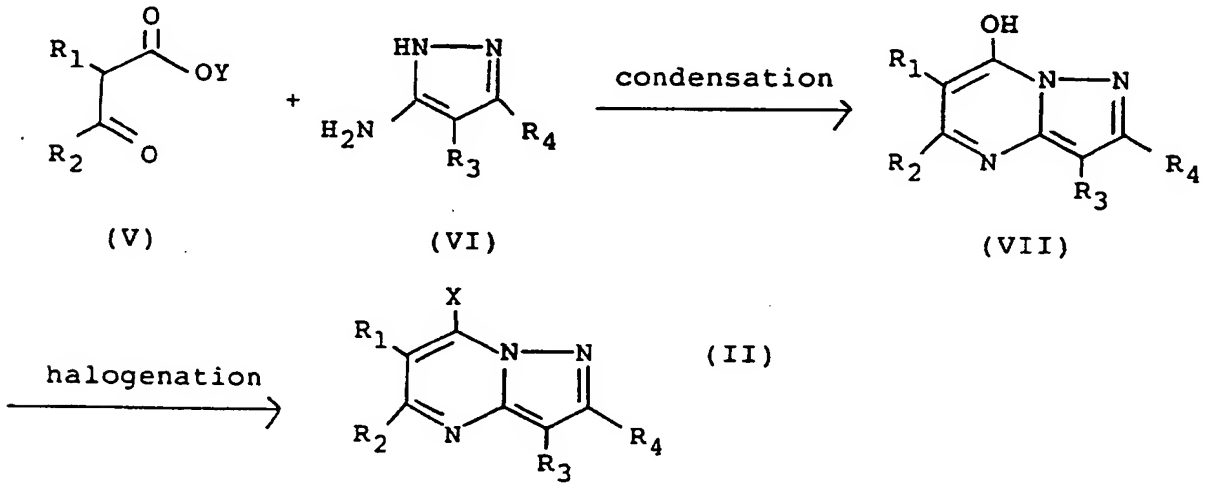
(Ic) (Id)

wherein Y_1 - Y_7 and Y'_1 - Y'_7 are each the corresponding group in the formula (I), that is, Y_1 and Y'_1, Y_2 and Y'_2, Y_3 and Y'_3, and Y_4 and Y'_4 are R_1, R_2, R_3 and R_4, respectively, Y_5 and Y'_5, Y_6 and Y'_6, Y_7 and Y'_7 are hydrogen atom, hydroxyl group, a lower alkyl group, a lower alkoxycarbonyl group or carboxy group, provided that at least one of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7 is carboxyl group, a lower alkoxycarbonyl group or a carboxy-lower alkyl group, and a group in Y'_1, Y'_2, Y'_3, Y'_4, Y'_5, Y'_6 and Y'_7, of which position is the same as the said group, is hydroxyl group or a hydroxy-lower alkyl group.

As shown in Reaction Scheme-3, one of the compounds of the present invention (Id) can be prepared by the reduction of the compound (Ic), which is one of the compounds (I) prepared in Reaction Scheme-1 and has a carboxyl group, a lower alkylcarbonyl group and/or a carboxy-lower alkyl group. The above reduction reaction is carried out in an inert organic solvent such as diethyl ether, THF, dioxane, etc., by using a suitable reducing agent such as lithium aluminum hydride, aluminum hydride, diborane, etc. in an amount of 1 to 10 moles to one mole of the compound (Ic). The reaction is carried out at a temperature of about 0 to 50 °C, preferably at a temperature of about 0 °C to room temperature.

In the above Reaction Scheme-1, the compound (II) used as a starting compound includes both a known compound and a novel compound, and these compounds may be prepared, for example, by a method disclosed in the following Reaction Scheme-4.

[Reaction Scheme-4]



(V) (VI) (VII) (II)

wherein Y is a lower alkyl group, and R_1, R_2, R_3, R_4 and X are the same as defined above.

The condensation reaction between the compound (V) and the compound (VI) in Reaction Scheme-4 is carried out in a solvent such as acetic acid, ethanol, etc., at a temperature of room temperature to a boiling point of the solvent.

The compound (V) is used in an amount of almost equimolar to the compound (VI), and the reaction is carried out for 2 to 5 hours to give the compound (VII).

Subsequently, the compound (II), the starting compound of the present invention, is prepared by halogenating the compound (VII).

The halogenation reaction is carried out by treating with a halogenating agent such as phosphorus oxychloride, phosphorus oxybromide, etc. in the presence of an acid acceptor such as N,N-dimethylaniline, N,N-diethylaniline, triethylamine, etc. Besides, the above halogenating agent may also be used as a solvent, and hence, the reaction does not need any solvent but can be carried out in another inert solvent such as benzene, toluene, xylene, etc.

Moreover, the acid acceptor is used in an amount of about 1 to 10 moles to 1 mole of the compound (VII).

The reaction is carried out at a temperature of room temperature to 100 °C, for 0.5 to two hours.

The compounds obtained in above Reaction Schemes 1 to 4 can be purified and isolated from the reaction system by a conventional separation method. The conventional method for isolating and purification is, for example, extraction with a solvent, distillation, recrystallization, column chromatography, preparative thin layer chromatography, and the like. The compounds of the present invention thus obtained may be isolated, if necessary, in the form of a free base, or in the form of an acid addition salt with a pharmaceutically acceptable acid such as inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, etc.) or organic acids (e.g. oxalic acid, fumaric acid, maleic acid, tartaric acid, citric acid, etc.), or in the form of a metal salt with a pharmaceutically acceptable alkali metals or alkaline earth metals (e.g. sodium, potassium, calcium, etc.).

The anti-inflammatory agent of the present invention is used in the form of a pharmaceutical preparation containing an effective amount of at least one of the above compounds (I') and salts thereof.

The pharmaceutical preparation form and the administration route of the present anti-inflammatory agent may be any conventional ones, but it is advantageous to administer the present anti-inflammatory agent locally in the form of an external preparation such as creams, ointments, lotions, aerosols, etc. These pharmaceutical preparations may be prepared by a conventional method with a conventional nontoxic pharmaceutical excipinent. The base for preparation of creams, ointments, etc. is, for example, white soft paraffine, paraffine, glycerin, bees wax, cellulose derivatives (e.g. methyl cellulose, etc.), glyceryl monostearate, cetostearyl alcohol, octyldodecanol, medium-chain fatty acid triglyceride, polyethyleneglycol, silicone, bentonite, and the like. In the liquid preparations (e.g. lotions, etc.) and aerosols, the solvent for dissolving an active ingredient includes, for example, water, ethyl alcohol, isopropyl alcohol, propyleneglycol, 1,3-butyleneglycol, polyethyleneglycol, crotamiton, and the like, and the surfactant includes, for example, sorbitan fatty acid esters, polyoxyethylenesorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene ethers of hydrogenated castor oil, lecithin, self-emulsifiable-type glyceryl monostearate, and the like. Moreover, the preparation of the present invention may be prepared in the form of a suspension, and the suspending agent includes, for example, cellulose derivatives (e.g. carboxymethyl cellulose sodium salt, methyl cellulose, etc.), and natural gums (e.g. tragacanth, gum arabic, etc.), and the like.

The present preparations thus prepared may contain a conventional preservative (e.g. p-hydroxybenzoic acid ester, benzalkonium chloride, sorbitan acid salt, etc.), or other various additives, if necessary.

The clinical dosage of the present anti-inflammatory agent varies depending on ages, weights, sensibility of the patients, and severities of the diseases, but it is usually in the range of about 0.001 to 10 g, preferably about 0.02 to 5 g per day for an adult. The dosage may, of course, be out of this range depending on the conditions of the patients.

Best Mode for Carrying Out the Invention

The present invention is illustrated in more detail by the following Examples wherein the present compounds are prepared, Preparations and Pharmacological experiments.

Example 1

Preparation of 7-(3,5-di-t-butyl-4-hydroxyphenyl)-aminopyrazolo[1,5-a]pyrimidine:

A suspension of 7-chloropyrazolo[1,5-a]pyrimidine (1.0 g), 3,5-di-t-butyl-4-hydroxyaniline hydrochloride (1.8 g) and diethylaniline (2.3 ml) in toluene (50 ml) is heated at 120 °C for 30 minutes. After cooling, the solvent is distilled off, and the residue is purified by silica gel column chromatography (solvent; $CHCl_3$) to give 7-(3,5-di-t-butyl-4-hydroxyphenyl)aminopyrazolo[1,5-a]pyrimidine (890 mg) as colorless crystal.

M.p. 264 - 266 °C (decomposed)

^{1}H-NMR ($CDCl_3$): δ

1.48 (s, 18H), 5.63 (s, 1H), 5.92 (s, 1H), 6.55 (d, J = 2.3 Hz, 1H), 7.47 (s, 2H), 8.14 (d, J = 2.3 Hz, 1H)

Example 2

Preparation of 5-methyl-7-(3,5-di-t-butyl-4-hydroxyphenyl)aminopyrazolo[1,5-a]pyrimidine:

A suspension of 5-methyl-7-chloropyrazolo[1,5-a]-pyrimidine (3.5 g) and 3,5-di-t-butyl-4-hydroxyaniline hydrochloride (6.0 g) and diethylaniline (6.0 g) in toluene (150 ml) is heated at 120 °C for 30 minutes, and cooled. The reaction mixture is poured into water, and extracted with dichloromethane. The organic layer is dried over anhydrous magnesium sulfate and concentrated. The residue is purified by silica gel column chromatography (solvent; dichloromethane/ethyl acetate/methanol = 5:1:1) to give the title compound (4.7 g) as colorless crystal.

M.p. 251 - 253 °C

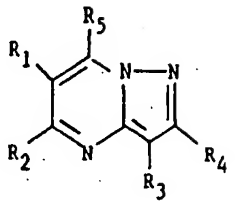
1H-NMR (DMSO-d_6, internal standard: TMS): δ

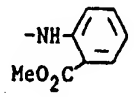
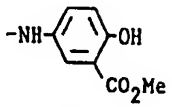
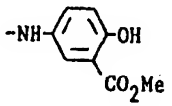
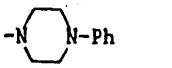
1.41 (s, 18H), 2.35 (s, 3H), 6.05 (s, 1H), 6.35 (d, J = 2.0 Hz, 1H), 7.18 (s, 2H), 8.09 (d, J = 2.0 Hz, 1H), 9.5 (brs, 1H)

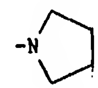
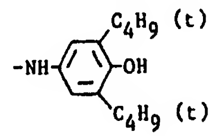
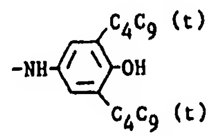
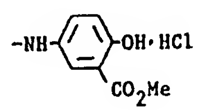
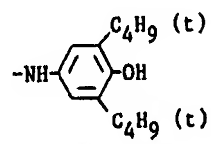
Examples 3 to 26

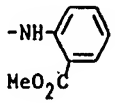
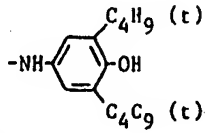
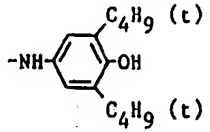
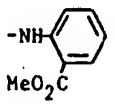
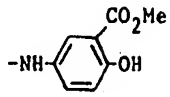
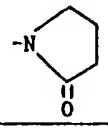
The compounds listed in the following Table 1 are obtained in the same manner as in Example 1.

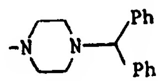
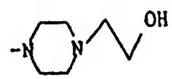
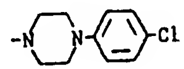
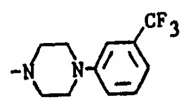
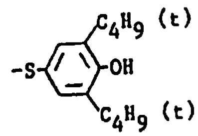
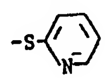
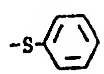
Table 1



Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	^{1}H-NMR δ value (internal standard: TMS)
3	H	Me	H	H		140-142	$CDCl_3$: 2.56 (s, 3H), 3.99 (s, 3H), 6.50 (d, J=2.3 H, 1H), 6.62 (s, 1H), 7.18 (t-d, J=7.3, 1.0 Hz, 1H), 7.64 (t-d, J=7.3, 1.7 Hz, 1H), 7.75 (d-d, J=7.3, 1.0 Hz, 1H), 8.1-8.2 (m, 2H)
4	H	Me	H	H		188-189	$CDCl_3$: 2.46 (s, 3H), 3.98 (s, 3H), 5.93 (s, 1H), 6.46 (d, J=2.5 Hz, 1H), 7.10 (d, J=8.9 Hz, 1H), 7.48 (d-d, J=8.9, 2.7 Hz, 1H), 7.85 (d, J=2.7 Hz, 1H), 7.86 (brs, 1H), 8.01 (d, J=2.5 Hz, 1H), 10.82 (s, 1H)
5	H	Me	H	Ph		245-246 (dec.)	$CDCl_3$-CD_3OD: 2.64 (s, 3H), 3.99 (s, 3H), 5.92 (s, 1H), 7.07 (s, 1H), 7.20 (d, J=8.8 Hz, 1H), 7.4-7.5 (m, 3H), 7.56 (d-d, J=8.8, 2.6 Hz, 1H), 7.95 (d, J=2.6 Hz, 1H), 8.0-8.1 (m, 2H)
6	H	Me	H	Ph		197-199	$CDCl_3$: 2.54 (s, 3H), 3.48 (t, J=5.0 Hz, 4H), 3.95 (t, J=5.0 Hz, 4H), 6.03 (s, 1H), 6.77 (s, 1H), 6.94 (t, J=7.2 Hz, 1H), 7.03 (d, J=8.4 Hz, 2H), 7.3-7.5 (m, 5H), 8.00 (d-d, J=7.2, 1.5 Hz, 2H)
7	H	Me	H	Ph		210-215 (dec.)	$CDCl_3$-CD_3OD: 2.52 (s, 3H), 2.69 (t, J=5.6 Hz, 2H), 2.85 (t, J=4.9 Hz, 4H), 3.76 (t, J=5.6 Hz, 2H), 3.86 (t, J=4.9 Hz, 4H), 6.05 (s, 1H), 6.74 (s, 1H), 7.3-7.5 (m, 3H), 7.98 (d, J=6.9 Hz, 2H)

Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	^{1}H-NMR δ value (internal standard: TMS)
8	H	Me	H	Ph		194-196	$CDCl_3$: 2.0-2.1 (m, 4H), 2.43 (s, 3H), 4.0-4.1 (m, 4H), 5.59 (s, 1H), 6.59 (s, 1H), 7.3-7.5 (m, 3H), 7.95 (d-d, J=7.6, 1.7 Hz, 2H)
9	H	Me	H	Ph		280-282 (dec.)	$CDCl_3$: 1.47 (s, 18H), 2.46 (s, 3H), 5.32 (s, 1H), 6.02 (s, 1H), 6.72 (s, 1H), 7.18 (s, 2H), 7.3-7.5 (m, 3H), 8.00 (d, J=8.1 Hz,2H)
10	H	Me	CO_2Et	H		213-215	DMSO-d_6: 1.31 (t, J=7.1 Hz, 3H), 1.40 (s, 18H), 2.49 (s, 3H), 4.26 (q, J=7.1 Hz, 2H), 6.22 (s, 1H), 7.14 (s, 1H), 7.16 (s, 1H), 8.48 (s, 1H), 9.83 (s, 1H)
11	H	Me	CO_2Et	H		208-210 (dec.)	$CDCl_3$: 1.41 (t, J=7.1 Hz, 3H), 2.63 (s, 3H), 2.67 (t, J=5.3 Hz, 2H), 2.79 (t, J=4.9 Hz, 4H), 3.70 (t, J=5.3 Hz 2H), 3.77 (t, J=4.9 Hz, 4H), 4.40 (q, J=7.1 Hz, 2H), 6.14 (s, 1H), 8.41 (s, 1H)
12	H	Me	CO_2Et	H		170-173	DMSO-d_6: 1.35 (t, J=7.2 Hz, 3H), 2.55 (s, 3H), 3.90 (s, 3H), 4.36 (q, J=7.2 Hz, 2H), 6.37 (s, 1H), 7.20 (d, J=8.9 Hz, 1H), 7.58 (d-d, J=8.9, 2.5 Hz, 1H), 7.81 (d, J=2.5 Hz, 1H), 8.69 (s, 1H)
13	H	Me	Ph	H		222-224	DMSO-d_6: 1.42 (s, 18 Hz), 2.44 (s, 3H), 6.12 (s, 1H), 7.10 (s, 1H), 7.19 (s, 2H), 7.17-7.22 (m, 1H), 7.40 (d-d, J=7.5, 7.5 Hz, 2H), 8.19 (d, J=7.5 Hz, 2H), 8.63 (s, 1H), 9.61 (s, 1H)

Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	1H-NMR δ value (internal standard: TMS)
14	H	Me	Ph	H		174-175	DMSO-d_6: 2.55 (s, 3H), 3.89 (s, 3H), 6.77 (s, 1H), 7.24 d-d, J=8.0, 8.0 Hz, 1H), 7.32 (d-d, J=8.0, 8.0 Hz, 1H), 7.45 (d-d, J=8.0, 8.0 Hz, 2H), 7.76 (d-d, J=8.0, 8.0 Hz, 1H), 7.89 (d, J=8.0 Hz, 1H), 8.06 (d, J=8.0 Hz, 1H), 8.18 (d, J=8.0 Hz, 2H), 8.71 (s, 1H), 11.00 (s, 1H)
15	CO_2Et	H	H	H		248-250 (dec.)	DMSO-d_6: 0.90 (t, J=7.2 Hz, 3H), 1.35 (s, 18 Hz), 3.56 (q, J=7.2 Hz, 2H), 6.61 (d, J=2.2 Hz, 1H), 6.98 (s, 1H), 7.00 (s, 2H), 8.23 (d, J=2.2 Hz, 1H), 8.42 (s, 1H), 10.26 (s, 1H)
16	CH_2CO_2Et	Me	H	H		190-192	$CDCl_3$: 1.16 (t, J=7.1 Hz, 3H), 1.42 (s, 18H), 2.42 (s, 3H), 3.34 (s, 2H), 4.01 (q, J=7.1 Hz, 2H), 5.29 (s, 1H), 6.46 (d, J=2.2 Hz, 1H), 7.05 (s, 2H), 7.98 (d, J=2.2 Hz, 1H), 8.01 (brs, 1H)
17	CO_2Et	H	Ph	H		97-100	DMSO-d_6: 1.17 (t, J=7.2 Hz, 3H), 3.83 (s, 3H), 4.14 (q, J=7.2 Hz, 2H), 7.16 (d, J=8.0 Hz, 1H), 7.2-7.3 (m, 2H), 7.44 (d-d, J=8.0, 8.0 Hz, 2H), 7.54 (d-d, J=8.0, 8.0 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 8.14 (d, J=8.0 Hz, 2H), 8.71 (s, 1H), 8.82 (s, 1H), 11.24 (s, 1H)
18	CO_2Et	H	Ph	H		189-191	DMSO-d_6: 1.14 (t, J=7.2 Hz, 3H), 3.88 (s, 3H), 3.98 (q, J=7.2 Hz, 2H), 6.99 (d, J=8.9 Hz, 1H), 7.24 (d-d, J=8.0, 8.0 Hz, 1H), 7.4-7.5 (m, 3H), 7.67 (d, J=3.0 Hz, 1H), 8.14 (d, J=8.0 Hz, 2H), 8.67 (s, 1H), 8.72 (s, 1H), 10.44 (s, 1H), 10.60 (brs, 1H)
19	H	Me	H	Ph		156-158	$CDCl_3$: 2.33 (quintet, J=7.5 Hz, 2H), 2.61 (s, 3H), 2.69 (t, J=7.5 Hz, 2H), 4.48 (t, J=7.5 Hz, 2H), 6.86 (s, 1H), 6.96 (s, 1H), 7.4-7.5 (m, 3H), 7.9-8.0 (m, 2H)

Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	^{1}H-NMR δ value (internal standard: TMS)
20	H	Me	H	H		140-142	$CDCl_3$: 2.51 (s, 3H), 2.66 (t, J=4.9 Hz, 4H), 3.72 (t, J=4.9 Hz, 4H), 4.34 (s, 1H), 5.95 (s, 1H), 6.43 (d, J=2.3 Hz, 1H), 7.2-7.5 (m, 10H), 7.95 (d, J=2.3 Hz, 1H)
21	H	Me	H	H		57-59	$CDCl_3$-CD_3OD: 2.53 (s, 3H), 2.67 (t, J=5.6 Hz, 2H), 2.81 (t, J=5.0 Hz, 4H), 3.7-3.8 (m, 6H), 6.06 (s, 1H), 6.45 (d, J=2.3 Hz, 1H), 8.01 (d, J=2.3 Hz, 1H)
22	H	Me	H	H		199-201	$CDCl_3$-CD_3OD: 2.55 (s, 3H), 3.41 (t, J=5.0 Hz, 4H), 3.88 (t, J=5.0 Hz, 4H), 6.11 (s, 1H), 6.47 (d, J=2.3 Hz, 1H), 6.94 (d, J=9.0 Hz, 2H), 7.26 (d, J=9.0 Hz, 2H), 8.04 (d, J=2.3 Hz, 1H)
23	H	Me	H	H		>223	$CDCl_3$-CD_3OD: 2.70 (s, 3H), 3.57 (t, J=5.1 Hz, 4H), 4.5-4.6 (br, 4H), 6.52 (s, 1H), 6.64 (d, J=2.1 Hz, 1H), 7.1-7.2 (br, 2H), 7.4-7.5 (br, 2H), 8.12 (d, J=2.1 Hz, 1H)
24	H	Me	H	H		194-196	$CDCl_3$: 1.48 (s, 18H), 2.43 (s, 3H), 5.63 (s, 1H), 5.92 (s, 1H), 6.55 (d, J=2.3 Hz, 1H), 7.47 (s, 2H), 8.14 (d, J=2.3 Hz, 1H)
25	H	Me	H	H		170-172	$CDCl_3$: 2.50 (s, 3H), 6.50 (s, 1H), 6.59 (d, J=2.3 Hz, 1H), 7.40 (d-d-d, J=7.6, 4.8, 1.0 Hz, 1H), 7.68 (d-t, J=7.6, 1.0 Hz, 1H), 7.81 (t-d, J=7.6, 1.8 Hz, 1H), 8.11 (d, J=2.3 Hz, 1H), 8.72 (d-d-d, J=4.8, 1.8, 1.0 Hz, 1H)
26	H	Me	H	H		165-166	$CDCl_3$: 2.41 (s, 3H), 5.89 (s, 1H), 6.56 (d, J=2.3 Hz, 1H), 7.5-7.7 (m, 3H), 7.7-7.8 (m, 2H), 8.14 (d, J=2.3 Hz, 1H)

Example 27

Preparation of 7-(2-carboxyphenyl)amino-5-methyl-pyrazolo[1,5-a]pyrimidine:

To a solution of 7-(2-methoxycarbonylphenyl)amino-5-methylpyrazolo[1,5-a]pyrimidine (1.0 g) prepared in Example 3 in ethanol (20 ml) is added a 5 % sodium hydroxide solution (30 ml), and the mixture is heated with stirring at 100 °C for one hour. After cooling, the mixture is evaporated to remove ethanol, and the residue is neutralized with a 10 % hydrochloric acid, and further the pH value of the mixture is adjusted to pH 4 with a saturated aqueous citric acid solution. The precipitated crystal is collected by filtration, and washed with water, ethanol and ethyl ether, and dried to give 7-(2-carboxyphenyl)amino-5-methylpyrazolo-[1,5-a]pyrimidine (970 mg) as colorless crystal.

M.p. 261 - 262 °C (decomposed)

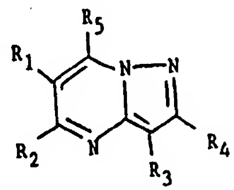
1H-NMR (DMSO-d_6): δ

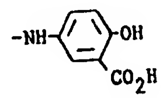
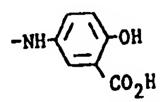
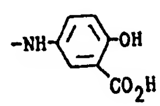
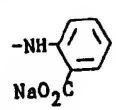
2.47 (s, 3H), 6.47 (d, J = 1.2 Hz, 1H), 6.76 (s, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 8.16 (d, J = 1.2 Hz, 1H)

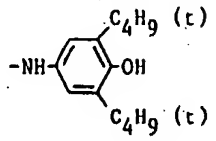
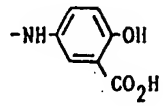
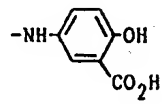
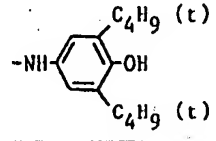
Examples 28 to 35

The compounds listed in the following Table 2 are obtained in the same manner as in Example 27.

Table 2



Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	^{1}H-NMR δ value (internal standard: TMS)
28	H	Me	H	H		284-285 (dec.)	$CDCl_3$-CD_3OD: 2.48 (s, 3H), 6.00 (s, 1H), 6.46 (d, J=1.8 Hz, 1H), 7.10 (d, J=9.2 Hz, 1H), 7.32 (d-d, J=9.2, 2.7 Hz, 1H), 7.92 (d, J=2.7 Hz, 1H), 8.06 (d, J=1.8 Hz, 1H)
29	H	Me	H	Ph		310-312 (dec.)	DMSO-d_6: 2.45 (s, 3H), 6.12 (s, 1H), 6.99 (s, 1H), 7.13 (d, J=8.7 Hz, 1H), 7.4-7.6 (m, 3H), 7.64 (d-d, J=8.7, 2.6 Hz, 1H), 7.87 (d, J=2.6 Hz, 1H), 8.16 (d, J=7.9 Hz, 2H)
30	H	Me	Ph	H		289-290 (dec.)	DMSO-d_6: 2.43 (s, 3H), 6.03 (s, 1H), 7.08 (d, J=8.8 Hz, 1H), 7.20 (d-d, J=8.0, 8.0 Hz, 1H), 7.40 (d-d, J=8.0, 8.0 Hz, 1H), 7.60 (d-d, J=8.8, 2.6 Hz, 1H), 7.82 (d, J=2.6 Hz, 1H), 8.18 (d, J=8.0 Hz, 2H), 8.66 (s, 1H), 9.84 (s, 1H)
31	H	Me	Ph	H		>300	DMSO-d_6: 2.53 (s, 3H), 6.79 (s, 1H), 7.06 (t, J=7.2 Hz, 1H), 7.18 (t, J=7.2 Hz, 1H), 7.4-7.5 (m, 3H), 7.66 (d, J=8.3 Hz, 1H), 8.05 (d, J=6.2 Hz, 1H), 8.85 (d, J=8.3 Hz, 2H), 8.60 (s, 1H), 14.42 (s, 1H)

Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	^{1}H-NMR δ value (internal standard: TMS)
32	H	Me	CO_2H	H		240-241 (dec.)	DMSO-d_6: 1.41 (s, 18H), 2.42 (s, 3H), 6.22 (s, 1H), 7.17 (s, 2H), 7.15 (s, 1H), 8.47 (s, 1H), 9.84 (s, 1H)
33	H	Me	CO_2H	H		227-228	DMSO-d_6: 2.40 (s, 3H), 6.12 (s, 1H), 7.04 (d, J=8.7 Hz, 1H), 7.53 (d-d, J=8.7, 2.7 Hz, 1H), 7.76 (d, J=2.7 Hz, 1H), 8.47 (s, 1H), 10.00 (brs, 1H)
34	CO_2H	H	Ph	H		254-255 (dec.)	DMSO-d_6: 6.89 (d, J=8.9 Hz, 1H), 7.25 (d-d, J=8.0, 8.0 Hz, 1H), 7.3-7.5 (m, 3H), 7.64 (d, J=2.7 Hz, 1H), 8.12 (d, J=8.0 Hz, 2H), 8.61 (s, 1H), 8.76 (s, 1H), 10.99 (s, 1H)
35	CH_2CO_2H	Me	H	H		252-254 (dec.)	DMSO-d_6: 1.35 (s, 18H), 2.32 (s, 3H), 3.25 (s, 2H), 6.39 (d, J=2.2 Hz, 1H), 6.87 (s, 2H), 6.99 (s, 1H), 8.04 (d, J=2.2 Hz, 1H), 8.95 (s, 1H)

Example 36

Preparation of 7-(3,5-di-t-butyl-4-hydroxyphenyl)-amino-3-hydroxymethyl-5-methylpyrazolo[1,5-a]pyrimidine:

To a suspension of $LiAlH_4$ (840 mg) in anhydrous ether (50 ml) is added dropwise a solution of 7-(3,5-di-t-butyl-4-hydroxyphenyl)amino-3-ethoxycarbonyl-5-methylpyrazolo[1,5-a]pyrimidine (3.5 g) prepared in Example 10 in dry THF (50 ml) with ice-cooling, and the mixture is stirred at the same temperature for 30 minutes, and further stirred at room temperature for one hour. To the mixture are added ethyl acetate and water to decompose excess $LiAlH_4$, and the mixture is filtered with celite. The filtrate is diluted with ethyl acetate, and washed with a saturated aqueous $Na_2S_2O_4$ solution and a saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The mixture is evaporated to remove the solvent, and the residue is purified by silica gel column chromatography (solvent; ethyl acetate/dichloroethane = 2:1 → chloroform/methanol = 8:1). The obtained crystal is washed with ethyl ether to give 7-(3,5-di-t-butyl-4-hydroxyphenyl)amino-3-hydroxymethyl-5-methylpyrazolo[1,5-a]pyrimidine (2.3 g) as colorless crystal.

M.p. 194-196 °C

^{1}H-NMR (DMSO-d_6): δ

1.41 (s, 18H), 2.36 (s, 3H), 4.60 (d, J = 5.2 Hz, 2H), 4.79 (t, J = 5.2 Hz, 1H), 6.04 (s, 1H), 7.10 (brs, 1H), 7.17 (s, 2H), 8.06 (s, 1H), 9.44 (brs, 1H)

Example 37

Preparation of 6,7-dihydro-8-(3,5-di-t-butyl-4-hydroxyphenyl)amino-5H-cyclopenta[d]pyrazolo[1,5-a]-pyrimidine:

Ethyl 2-oxocyclopentanecarboxylate (31 g) and 3-aminopyrazole (17.4 g) are dissolved in acetic acid (300 ml), and the mixture is heated at 100 °C for 3 hours. After allowed to stand for cooling, the resulting crystal is collected by filtration, and washed successively with water and diethyl ether, and further recrystallized from dichloromethane-diethyl ether to give a crystal (22.3 g) having a melting point of more than 280 °C.

Subsequently, the crystal obtained above (9 g) and N,N-diethylaniline (15 ml) are added to phosphorus oxychloride (90 ml), and the mixture is heated at 80 °C for three hours. After the reaction is complete, the mixture is concentrated under reduced pressure, and the residue is poured into ice-water, and extracted with dichloromethane. The organic layer is washed with a saturated sodium chloride solution. The residue is dried over anhydrous sodium sulfate, and evaporated to remove the solvent. The residue is crystallized from n-hexane to give a crystal (9.9 g).

The above crystal (3.9 g), 3,5-di-t-butyl-4-hydroxyaniline hydrochloride (5.2 g) and N,N-diethylaniline (5 ml) are added to toluene (60 ml), and the mixture is heated at 100 °C for three hours. The mixture is treated in the same manner as in Example 1, and the resulting crude product is purified by silica gel column chromatography (solvent; dichloromethane → dichloromethane/methanol = 50:1), and further recrystallized from dichloromethane/diethyl ether to give the desired compound (3.8 g).

M.p. 255 - 257 °C (decomposed)

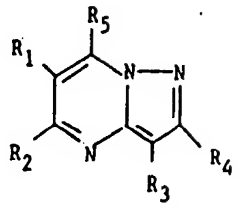
^{1}H-NMR ($CDCl_3$): δ

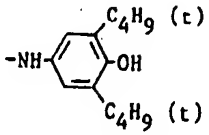
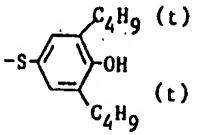
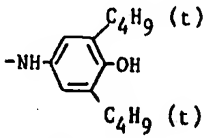
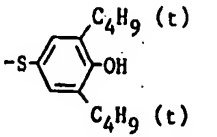
1.45 (s, 18H), 1.96 (quintet, J = 7.3 Hz, 2H), 2.22 (t, J = 7.3 Hz, 2H), 2.89 (t, J = 7.3 Hz, 2H), 5.30 (s, 1H), 6.40 (d, J = 2.3 Hz, 1H), 7.07 (s, 2H), 7.97 (d, J = 2.3 Hz, 1H), 7.97 (brs, 1H)

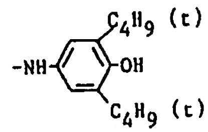
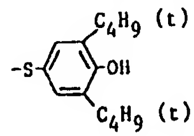
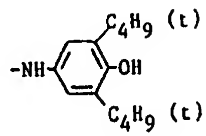
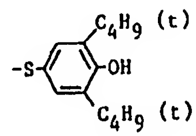
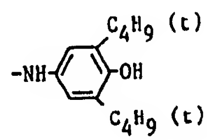
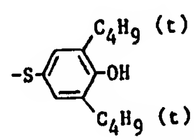
Example 38 - 48

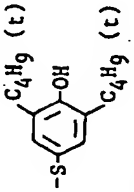
The compounds listed in the following Table 3 are obtained in the same manner as in Example 37.

Table 3



Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	^{1}H-NMR δ value (internal standard: TMS)
38	H	$-(CH_2)_3CH_3$	H	H		200-202	$CDCl_3$: 0.93 (t, J=7.3 Hz, 3H), 1.3-1.5 (m, 2H), 1.47 (s, 18H), 1.6-1.8 (m, 2H), 2.69 (t, J=7.8 Hz, 2H), 5.28 (s, 1H), 6.10 (s, 1H), 6.46 (d, J=2.3 Hz, 1H), 7.17 (s, 2H), 7.85 (brs, 1H), 8.01 (d, J=2.3 Hz, 1H)
39	H	$-(CH_2)_3CH_3$	H	H		155-157	$CDCl_3$: 0.88 (t, J=7.3 Hz, 3H), 1.2-1.4 (m, 2H), 1.47 (s, 18H), 1.5-1.7 (m, 2H), 2.65 (t, J=7.6 Hz, 2H), 5.63 (s, 1H), 5.92 (s, 1H), 6.57 (d, J=2.4 Hz, 1H), 7.48 (s, 2H), 8.14 (d, J=2.4 Hz, 1H)
40	H	Ph	H	H		212-214	$CDCl_3$: 1.48 (s, 18H), 5.31 (s, 1H), 6.61 (d, J=2.2 Hz, 1H), 6.65 (s, 1H), 7.24 (s, 2H), 7.4-7.5 (m, 3H), 7.9-8.0 (m, 3H), 8.07 (d, J=2.2 Hz, 1H)
41	H	Ph	H	H		229-231	$CDCl_3$: 1.49 (s, 18H), 5.65 (s, 1H), 6.55 (s, 1H), 6.72 (d, J=2.4 Hz, 1H), 7.4-7.5 (m, 3H), 7.55 (s, 2H), 7.7-7.8 (m, 2H), 8.21 (d, J=2.4 Hz, 1H)

Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	^{1}H-NMR δ value (internal standard: TMS)
42	H	$-CH(CH_3)_2$	H	H		220-224 (dec.)	$CDCl_3$: 1.30 (d, J=6.9 Hz, 6H), 1.47 (s, 18H), 2.97 (septet, J=6.9 Hz, 1H), 5.27 (s, 1H), 6.18 (s, 1H), 6.48 (d, J=2.3 Hz, 1H), 7.19 (s, 2H), 7.88 (brs, 1H), 8.01 (d, J=2.3 Hz, 1H)
43	H	$-CH(CH_3)_2$	H	H		185-187	$CDCl_3$: 1.17 (d, J=6.9 Hz, 6H), 1.47 (s, 18H), 2.91 (septet, J=6.9 Hz, 1H), 5.62 (s, 1H), 5.92 (s, 1H), 6.58 (d, J=2.3 Hz, 1H), 7.48 (s, 2H), 8.14 (d, J=2.3 Hz, 1H)
44	H	Et	H	H		230-232	$CDCl_3$: 1.30 (t, J=7.6 Hz, 3H), 1.47 (s, 18H), 2.73 (q, J=7.6 Hz, 2H), 5.28 (s, 1H), 6.12 (s, 1H), 6.46 (d, J=2.3 Hz, 1H), 7.18 (s, 2H), 7.87 (brs, 1H), 8.01 (d, J=2.3 Hz, 1H)
45	H	Et	H	H		213-214	$CDCl_3$: 1.20 (t, J=7.6 Hz, 3H), 1.47 (s, 18H), 2.69 (q, J=7.6 Hz, 2H), 5.62 (s, 1H), 5.94 (s, 1H), 6.57 (d, J=2.3 Hz, 1H), 7,48 (s, 2H), 8.14 (d, J=2.3 Hz, 1H)
46	H		H	H		221-223	$CDCl_3$: 0.9-1.1 (m, 4H), 1.47 (s, 18H), 1.9-2.0 (m, 1H), 5.29 (s, 1H), 6.03 (s, 1H), 6.38 (d, J=2.1 Hz, 1H), 7.17 (s, 2H), 7.83 (brs, 1H), 7.97 (d, J=2.1 Hz, 1H)
47	H		H	H		206-207	$CDCl_3$: 0.9-1.0 (m, 4H), 1.49 (s, 18H), 1.85 (quintet, J=6.5 Hz, 1H), 5.62 (s, 1H), 5.84 (s, 1H), 6.48 (d, J=2.3 Hz, 1H), 7.48 (s, 2H), 8.10 (d, J=2.3 Hz, 1H)

Ex. No.	R_1	R_2	R_3	R_4	R_5	M.p. °C	1H-NMR δ value (internal standard: TMS)
48	$-CH_2-CH_2-CH_2-$		H	H		209-210 (dec.)	$CDCl_3$: 1.44 (s, 18H), 1.91 (quintet, J=7.4 Hz, 2H), 2.07 (t, J=7.4 Hz, 2H), 2.87 (t, J=7.4 Hz, 2H), 5.54 (s, 1H), 6.53 (d, J=2.3 Hz, 1H), 7.49 (s, 2H), 8.09 (d, J=2.3 Hz, 1H)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 6, because they relate to subject matter not required to be searched by this Authority, namely:

Claim 6 pertains to a medical treatment of a human body.

2. [ ] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.